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EXAMINER	
HAMUD, FOZIA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,818	BAKER ET AL.	
	Examiner	Art Unit	
	FOZIA M. HAMUD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *28-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims:

1. Claims 28-32 are pending and under consideration.

Specification:

2. Applicants' amendment to the specification filed on 12 December 2007, amending the title of the invention is acknowledged. No new matter is added.

Claim Rejections - 35 U.S.C. §101/112, first paragraph:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 28-32 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility. Claims 28-32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. see the office actions mailed on 06/12/2007, 04/03/2006, 01/03/2005, 11/24/2004 and 03/19/2004.

A portion of the basis for these rejections is withdrawn. Specifically, the Examiner no longer asserts that mRNA levels are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., Haynes et al., Gygi et al., Lian et al., Fessler et al. The mRNA/polypeptide correlation issue will no longer be addressed. The basis of the maintained rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to an isolated antibody that specifically binds to the polypeptide of SEQ ID NO:77, which is a monoclonal antibody, humanized, an antibody fragment or labeled.

Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. The specification discloses that the gene encoding PRO1293 was amplified in one primary lung tumor (HF-000840) and two colon tumors, (HF:000539, and HF-000795), (see page 503, column 1). The specification teaches that HF-000840 is a primary lung tumor and that HF-000539 and HF-000795 are colon tumor "centers", (see page 507, lines 5-12). However, there is no description of the type of lung tumor (adenocarcinoma or squamous, cell carcinoma or large cell carcinoma for example) or colon tumor or what cancer stage were these samples. The specification provides no details regarding the types or stages of lung or colon tumors these samples are, such information is provided for other tumors at page 499, table 7.

The specification asserts that gene amplification is associated with over-expression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung and other cancers, (page 494, lines 20-25). The specification also generally asserts that the polypeptides are useful as diagnostics for cancer. However, the instant specification does not demonstrate that the PRO1293 polypeptide is actually overly expressed in any of the cancers mentioned. Applicants have not shown that there is a relationship between DNA amplification and increased amounts of corresponding mRNA, protein or antibody. Although the data in the instant specification shows that gene copy number is increased in certain tumor tissue samples, it does not necessarily follow that an increase in gene copy (DNA) number results in increased gene expression (mRNA) and increased protein expression, such that the polypeptide of SEQ ID NO:77, or antibodies that bind it, would be useful diagnostically or as target for cancer drug development. In order for PRO1293 polypeptides to be overexpressed in lung or colon tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed.

Response to Applicants' Arguments:

4. Applicants submit that the PTO has not established a prima facie case for lack of utility and that the polypeptides of claims 28-32 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed polypeptides without any further experimentation. Applicants submit

that the gene amplification data disclosed in Example 143 establishes a credible, substantial and specific patentable utility for the PR01293 polypeptides and antibodies that bind them, and the gene amplification data for the gene encoding the PRO 1293 polypeptide is clearly disclosed in the instant specification under Example 143. Applicants argue that as previously discussed, ΔCt value of at least 1.0 was observed for PRO1293 in at least three of the tumors listed in Table 8. PRO1293 showed approximately 1.71 ΔCt units which corresponds to $2^{1.7l}$ fold amplification or 3.27 fold amplification in primary lung tumor (HF-000840), and approximately 1.13-2.33 ΔCt units which corresponds to $2^{1.13}$ -$2^{2.33}$ fold amplification or 2.19 fold to 5.03-fold amplification in colon tumors (HF-000539 and HF-000795).

Applicants maintain that the specification discloses at least one credible, substantial and specific asserted utility for the PRO 1293 polypeptides and antibodies that bind them for the reasons previously set forth in Applicants' Appeal Brief filed 26 July 2005. Applicants argue that although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft et al, Hyman et al., Pollack et al., the Goddard Declarations and the two Polakis Declarations, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Applicants conclude that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed and antibodies the

bind it would have utility in the diagnosis of lung and colon cancer. Applicants further contend that they have submitted over a hundred references, along with Declarations of Dr. Paul Polakis (made of record in the Preliminary Amendment of March 9, 2007 and Response of August 19, 2004), which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants submit that it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist. The law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist.

These arguments have been considered, but are not deemed persuasive. Applicants have not shown that the encoded polypeptide is amplified. At page 498 ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 498, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. First, there are several problems with the data provided in this example. Only two uncharacterized lung cancer samples and one uncharacterized colon cancer sample out of the couple of dozen samples tested positive. Therefore, if a sample were taken from an individual with lung cancer or colon cancer for diagnosis, it is more likely than not

that this assay would yield a false negative result. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. Similarly, pre-malignant lesions and ulcerative colitis have been associated with aneuploidy in colon tissue. See Fleischhacker et al., 1995, Modern Pathology 8:360-365, especially p. 360, 1st paragraph of introduction. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor or colon tumor samples and normal lung epithelium or normal colon and does not correct for aneuploidy. Thus it is not clear that PRO1293 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium, or in cancerous colon tissue more than in damaged (non-cancerous) colon tissue. One skilled in the art would not conclude that antibodies that bind PRO1293 are diagnostic probes for lung cancer or colon cancer unless it is clear that PRO1293 is amplified to a clearly greater extent in true lung tumor or colon tumor tissue relative to non-cancerous lung epithelium or colon tissue.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of lung tumor or colon tumor samples had tested positive, the data have no bearing on the utility of the claimed PRO1293 polypeptides. In order for PRO1293 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide

levels. No data regarding PRO1293 mRNA or PRO1293 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between mRNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of WISP-1 gene amplification and expression in human colontumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of WISPs in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

The general concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general

lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDXl, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." (emphasis added). The protein encoded by the DDX gene had been characterized as being a putative RNA helicase, a type of enzyme that would be expected to confer a selective advantage to the cells in which it (the DDX gone) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "**It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gone-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1293 confers any growth advantage to a cell, and thus it

cannot be presumed that the protein is overexpressed because the genomic DNA including the gone being studied gone is amplified.

An additional reference that provides evidence that gone amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628). 2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but lack biological relevance in terms of the development of lung adenocarcinoma." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that it is more likely than not that gene amplification does NOT correlate with increased protein levels, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO1293. Therefore, data pertaining to PRO1293 genomic DNA do not indicate anything significant regarding the claimed PRO1293 polypeptides. The data do not support the specification's assertion that PRO1293 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1293 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1293

polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of antibodies that bind the PRO1293 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al., the rejections are properly maintained.

Applicants point out that Hanna et al. clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna et al. p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus, Applicants contend that Hanna et al. support Applicants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression. Applicants submit that they have clearly shown that the gene encoding the PRO1293 polypeptide is amplified in a number lung and colon tumors and cell lines. Therefore, the PRO1293 gene, similar to the HER-2/neu gene disclosed in Hanna et al., is a tumor associated gene. Applicants argue that in the majority of

amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1293 gene, that the PRO1293 polypeptide is concomitantly overexpressed. Regarding Pennica et al and Konopka et al., Applicants argue that the Examiner asserts that "Pennica and Konopka suffice to show that DNA amplification is not always associated with overexpression of the gene product. Applicants submit that nowhere in either the Pennica or Konopka papers do the authors suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. On the contrary, there is a statement in Pennica that says "[a]n analysis of WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and over-expression.

These arguments have been considered, but are not deemed persuasive. The Hanna et al reference addresses HER-2/neu gene which has been shown to be overexpressed in 10%-30% of invasive breast cancer patients and 40-60% of intraductal breast carcinoma. The protein encoded by the Her-2/neu has also been shown to also be over expressed in breast cancer. Thus, the Hanna et al is pertained to a well characterized gene that has been shown to be consistently over expressed in breast cancer. Hanna et al. provides another important example of a lack of correlation between gene amplification and mRNA/protein overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna et al. evidences that the

level of protein expression must be tested empirically to determine whether or not the protein can be used as a diagnostic marker for a cancer. The instant invention differs from Her-2/neu, because the instant specification has not shown that the protein encoded by PRO1293 gene is also over expressed in lung or colon cancer, and thus the skilled artisan must perform additional experiments, as directed by the art. Furthermore, it is acknowledged that Her-2/neu measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated. However, the amplification of the PRO1293 gene has never been compared to the overexpression of the PRO1293 polypeptide. The fact that the gene encoding the PRO1293 polypeptide is amplified in lung or colon tumors has never been questioned. However, Applicants have not shown that the encoded polypeptide is also amplified. The issue is not the number of samples tested positive, but that there is no indication that the polypeptide is also amplified. Applicants' utility standard would mandate only a showing that it is "not implausible" that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Applicants could obtain patent rights to "inventions" based on a disclosure consisting of little more than guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in Brenner v. Manson:

> "…a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy."

Applicants have not tested PRO1293 polypeptide expression therefore, Applicants have not been able to show that the PRO1293 polypeptide is over- expressed in these colon and lung tumors. In the absence of any information regarding PRO1293 polypeptide expression the examiner considers the asserted utilities for the claimed antibodies are not be specific and substantial because a skilled artisan would not know if or how PRO1293 polypeptide expression changes in cancer. Pennica et al state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Phl template" (see abstract). The Pennica and Konopka reference shows that it is more likely than not that altered mRNA levels does not correlate with altered protein levels, (see above). Konopka et al. show only that, of the cell lines known to have increased abl protein expression, only one had amplification of the abl gene (page 4051, col. 1). This result proves only that increased mRNA and protein expression levels can result from causes other than gene amplification. Konopka et al. do not demonstrate that when gene amplification does occur, it does not result in increased mRNA and protein expression levels.

Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is overexpressed in cancer, it is more likely than not that

the encoded protein will also be expressed at an elevated level. It is "more likely than not" for amplified genes to have increased mRNA and protein levels Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft et al., Hyman et al., and Pollack et al., and the articles by Bea et al. and Godbout et al. (made of record in Preliminary Amendment of March 9, 2007) collectively teach that in general, gene amplification increases mRNA expression.

These arguments have been considered, but are not deemed persuasive. Firstly, the Examiner has not misinterpreted the scientific data presented, but has scientific data that support “it is more likely than not” that a gene amplified in cancer would not result in the amplification of the corresponding polypeptide, see Pennica et al., Konopka et al., Sen, Hittelman, Godbout et al., and Li et al, (discussed above). With respect to the Polakis Declarations filed by Applicant, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paraqon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.19 fold to 5.03-fold amplification of the gene encoding PRO1293 in two lung tumors and one colon tumor is significant. The significance can be questioned

based on the absence of factual support for the expert's opinion. In the instant case, the facts are that eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO1293, and the control used was not a matched non-tumor lung or non-tumor colon sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the antibodies that bind PRO1293 polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data.

Applicant urges that Orntoft et al. looked at the correlation of mRNA levels and protein expression for individual genes. Applicant urges that Orntoft et al. find that there is a highly significant correlation between mRNA and protein alterations. Applicant argues that a correlation in 39 out of 40 gene examined supports their position that mRNA correlates with protein levels. This has been fully considered but is not found to be persuasive. First, the rejection is no longer based on the issue of whether or not mRNA levels are predictive of protein levels. Therefore, these findings of Orntoft et al. are no longer relevant to the rejection. Regarding the correlation of gene amplification with increased protein levels, Orntoft et al. could only compare the levels of about 40 well-resolved and focused abundant proteins." (See abstract.) Moreover, Orntoft et also only concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO1293 in the instant specification. That is, it is not clear whether or not PRO1293 is in a gene

cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al.'s. results cannot be extended to the instant gene and protein.

Applicant urges that their more recent references (Orntoft et al., Hyman et al., Pollack et al.) must be acknowledged as more accurately reflecting the state of the art. This has been fully considered but is not found to be persuasive. Regarding Hyman et al. and Pollack et al., it is noted that Hyman et al. used CGH approach in their research, which is not comparable to the instant data for PRO1293. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also does not support the asserted utility of the claimed invention. Importantly, none of the three papers (Orntoft et al., Hyman et al., and Pollack et al.) reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1293 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

On page 20 of the response, Applicants bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal

No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9 of the Decision). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO1293 polypeptide to refute Applicants' assertion of a correlation between mRNA levels and protein expression.

The decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469) is irrelevant to the current situation, because this decision pertains to the correlation between mRNA levels and protein expression, and does not address correlation between genomic DNA levels and protein expression.

Applicants have submitted over a hundred references, along with the Declarations of Dr. Paul Polakis with their Preliminary Amendment filed on March 9, 2007, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants address Polakis Declaration. With respect to the Polakis II Declaration, the Examiner asserts that the fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between a change, if any, in PR01293 transcripts and PR01293 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist. Dr. Polakis' Declarations provide evidence, in the form of statements by an expert in the art.

The Polakis declarations pertain to the correlation between mRNA levels and protein levels, however, they do not speak to whether or not amplified genomic DNA levels correlate with increased levels of the encoded proteins. The claims under examination are directed to antibodies that bind the polypeptide of SEQ ID NO:77, and Applicants have not shown that amplification of the genomic DNA encoding PRO1293 in lung and colon tumor samples, results in amplification of the polypeptide.

Applicants cited 118 additional references to support their position that, in general, amplification of a particular gene leads to a corresponding change in the level of expression of the mRNA and encoded protein, the Examiner asserts that "none of the cited references address the major issue in this rejection, which is whether or not the PR01293 gene amplification in lung and colon tumor leads to overexpression of the PR01293 polypeptide in said tumors. Applicants submit that 118 references do not need to provide any data specific for PRO1293 because the data was provided as a proof of existence of a general correlation (more likely than not) between mRNA and protein expression for any given gene. Applicants are not required either under the law or under the Utility Guideline to prove that there is "absolute certainty" that mRNA/protein correlation exists for PRO 1293. Therefore, Applicants should not be required to provide any specific information for PRO1293, such as the sequences that are represented by the UNQ numbers; the objective staining intensity; the absolute magnitude of the mRNA and protein were overexpressed, etc.

Regarding, the 118 additional references referred to by Applicants, although, these references need not provide specific data for the PRO1293 polypeptide, they

need to provide support that a correlation (more likely than not) exists between gene amplification and protein expression. It appears that these references pertain to correlation between mRNA and protein, which is no longer the basis of the instant rejection.

Finally, further research needs to be done to determine whether the purported amplification of PRO1293 gene in lung and colon tumors supports a role for the peptide and antibodies that bind it in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial.

Conclusion:

5. No claim is allowed.

No new rejections have been made. THUS, THIS ACTION IS MADE FINAL. However, since new publications have been cited to support the maintained rejections, Applicant is assured that any new evidence specifically addressing the Hittelman, Sen, Fleischhacker, Godbout et al or Li et al references will be entered after final and given full consideration. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fozia Hamud
Patent Examiner
Art Unit 1647
09 March 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646